Editorial Commentary

Immunotherapy in cervical cancer: the advent of precision medicine

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Cervical cancer continues to be one of the most frequently diagnosed malignancy in women and infection with human papilloma virus (HPV) represents its greatest risk factor (1). Surgery, radiotherapy, systemic therapy or a combination of these therapeutic modalities are all considered standard of care in cervical cancer management based on clinical stage categories at diagnosis (2). However, clinical outcomes remain poor, especially in locally advanced and recurrent/metastatic disease (3). In the latter setting, systemic chemotherapy based on paclitaxel and cisplatin or the combination of the doublet chemotherapy and bevacizumab have shown a median overall survival (OS) up to 18 months (4,5). But once progression occurs, the possibility of additional treatment options is very limited (2).

In this context, we read with interest the interim analysis by Chung *et al.* (6) regarding the antitumor activity and safety of pembrolizumab in previously treated patients with advanced cervical cancer. The authors analyzed cervical cancer subpopulation in the phase II KEYNOTE-158 basket study. In total, 98 women were treated with pembrolizumab 200 mg intravenously every 3 weeks for up to 35 administrations, or until disease progression, intolerable toxicity, physician or patient decision (6). Objective response rate (ORR) was the primary outcome. Programmed death ligand 1 (PD-L1) positive population was identified, and defined on combined positive score (CPS) ≥1 (6). Tumor PD-L1 expression was positive in 82 cases (83.7%). The ORR, including the percentage of cases with partial or complete response defined by tumor size reduction (RECIST), was 12.2% (n=12). Responses lasted 9 months or more in 75% (n=9) of patients who had a response. There were 3 complete and 9 partial responses. All these responses were recorded in PD-L1-positive disease, accounting for an ORR rate of 14.6% in this subgroup (95% CI, 7.8 to 24.2). This setting of patients had also a longer median OS than patients with PD-L1-negative tumors (11 *vs.* 9.4 months). Overall, disease control rate was achieved in 30% of patients and after a median follow-up of 10.2 months, median duration of response had not been reached. The safety profile, in accordance with previous studies (7), was manageable and acceptable, with 12 episodes (12.2%) of severe adverse events.

The authors have to be congratulated for having achieved these results, which lead the Food and Drug Administration (FDA) to grant pembrolizumab accelerated approval for advanced PD-L1 positive cervical cancer indication. Indeed, the current approved combination of bevacizumab with chemotherapy for advanced/recurrent cervical cancer allows a significant increase of OS but without any predictive biomarker of response and at the price of a higher toxicity (increased incidence of grade 3 or greater thromboembolism, gastrointestinal events and genitourinary fistulas) (5).

More importantly, the main achievement of the

KEYNOTE-158 study is the pre-treatment identification of a group of patients (those expressing PD-L1) who derived the greatest benefit from pembrolizumab's administration, which represents the first step toward personalized treatment in cervical cancer management. Finally, longer duration of response and 30% disease control rate should be underlined, as they have recently emerged to contribute to long-term benefit and OS (8,9) and might be considered as a measure of disease control and symptom-free time prolongation.

On the other side, some limitations of the study have to be underscored, in order to further improve our next trial design. Actually, the KEYNOTE-158 study is a phase II basket clinical trial, evaluating predictive biomarkers in subjects with multiple types of advanced and/or metastatic solid tumors, that have progressed on standard of care therapy (10). This type of clinical study design, focusing on one targeted therapy against single biomarker only, without considering intratumoral heterogeneity and interpatient heterogeneity, may introduce biases and serious indirectness. The FDA's granted accelerated approval of pembrolizumab in cervical cancer was based on data from 77 patients with PD-L1 cervical cell cancer who were enrolled in 42 sites in 17 countries over the world. For instance, it is difficult to say which histology benefitted more (squamous or adenocarcinoma), because despite the original KEYNOTE-158 eligibility criteria for the cervical cancer cohort included histologically or cytologically-documented squamous cell carcinoma (10), actually 6 patients were enrolled regardless of histological diagnosis (adenosquamous n=1 and adenocarcinoma n=5) (6). This freedom for unexplained modifications in the protocol could be a relevant warning to scientific quality assessment. Moreover, initial final data collection date for primary outcome measure was scheduled on August 2023 (10). Lastly, it should be considered that the vast majority of patients expressed PD-L1, according to the CPS. Nonetheless, from a practical standpoint, a different cut-off for PD-L1 expression, might allow higher specificity and could positively influence treatment efficacy. This assumption remains hypothetical and needs confirmation.

Despite these clarifications regarding trial design, the results of the KEYNOTE-158 study are important to the oncology community, and the battle for availability of the drug available has already started. Surely, management of patients with advanced cervical cancer is evolving over the years and new treatment approaches are needed in recurrent/metastatic disease. The challenge toward precision medicine has started in all cancers and have to be pursued even in those extremely difficult and more demanding populations.

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Footnote

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